11-21-05

AF/1624
JFW

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/980,680-Conf. #6805
Filing Date	October 31, 2001
First Named Inventor	Paul L. Feldman
Art Unit	1624
Examiner Name	B. L. Coleman
Total Number of Pages in This Submission	
Attorney Docket Number	61036(71095)

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Return Receipt Postcard; Letter to USPTO

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	EDWARDS ANGELL PALMER & DODGE LLP		
Signature			
Printed name	Peter F. Corless		
Date	November 18, 2005	Reg. No.	33,860

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV754867265US, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: November 18, 2005 Signature: Susan M Dillon (Susan Dillon)

Docket 61036 (71095)
Express Mail Label No. EV754867265US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application:	P. Feldman, et al.		
Serial No.:	09/980,680	Examiner:	B. Coleman
Filing Date:	31 Oct 2001	Art Unit:	1624
For:	SHORT-ACTING BENZODIAZEPINES		

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

LETTER

Applicants filed an Amendment dated November 10, 2005 for the above-identified application.

Applicants enclose herewith a copy of Khan et al., Organic Preparations and Procedures Int., 10(3):105-111 (1978) which was requested in the prior Office Action.

Dated: November 18, 2005

Respectfully submitted,

By _____

Peter F. Corless
Registration No.: 33,860
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444
Attorneys/Agents For Applicant

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV754867265US, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: November 18, 2005 Signature: Susan M Dillon (Susan Dillon)

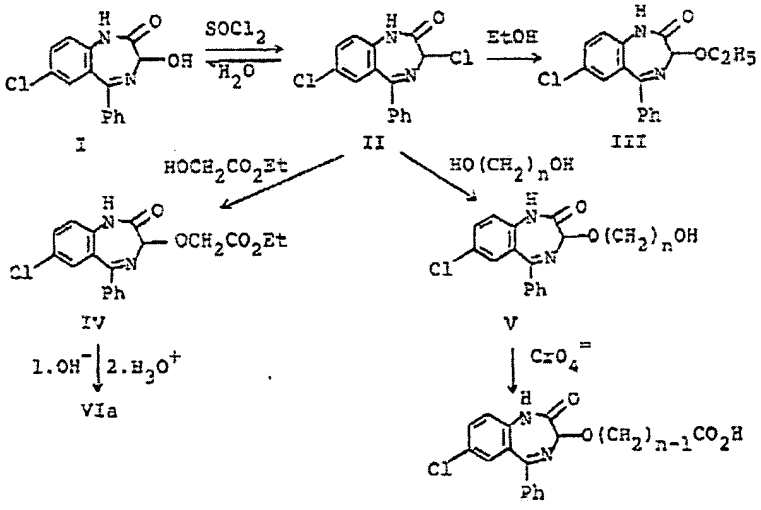
ORGANIC PREPARATIONS AND PROCEDURES INT. 10(3), 105-111 (1978)

SYNTHESIS OF 3-SUBSTITUTED 1,4-BENZODIAZEPINE-2-ONES†

Wajid A. Khan and Prithipal Singh*
Syva Research Institute
Palo Alto, California 94304

Page
149
137
105
123
133
137
143
149
143

Since the discovery of 1-methyl-7-chloro-2,3-dihydro-5-phenyl-1,4-benzodiazepine-2-one (diazepam) by Sternbach as a potent antianxiety agent and anticonvulsant a considerable number of 1,4-benzodiazepine derivatives have been reported in the literature.[1] During the course of some other studies, we



a) n = 2 b) n = 3 c) n = 4

needed 3-O-(carboxymethyl) derivative VIa of 7-chloro-3-hydroxy-2,3-dihydro-5-phenyl-1,4-benzodiazepine-2-one (oxazepam, I). Preparation of this compound from I in an overall

yield of 17% has been reported by Bell and coworkers.[1c] Their method involved the reaction of 3,7-dichloro-2,3-dihydro-5-phenyl-1,4-benzodiazepine-2-one (II) with ethyl glycolate followed by saponification of the product to VIa. In our hands the method, however, afforded only traces of the required product. We have developed a convenient and general method for preparation of acid VIa and its analogs in high yield and would like to report our findings.

Reaction of oxazepam I with thionyl chloride gave quantitatively the 3-chloro compound II as a pale yellow solid, mp. 139-140° (dec.), lit.[2,3] mp. 151-153° (dec.) and 120-121° (dec.) which slowly hydrolyzed back to I with moisture and gave ethoxy compound III with ethanol.[2] The chloro compound II was added slowly to an excess of vigorously stirred ethylene glycol at room temperature. The reaction mixture was diluted with water and extracted with organic solvents to afford exclusively the 1:1 product Va in 97% yield. In contrast, treatment of II with ethyl glycolate afforded only traces of IV. This is presumably due to the poor nucleophilicity of the hydroxyl group of ethyl glycolate as compared to that of the hydroxyl groups of ethylene glycol. Oxidation of Va with Jones reagent furnished the target acid VIa mp. 218-220° (dec.), lit.[1c] mp. 205-207°. It showed the expected IR and NMR data (Table 1) and was further characterized as its benzamide derivative. The overall yield of pure VIa from I was 70%. The generality of the reaction was demonstrated by high yield conversions of II to alcohols Vb and Vc and to acid VIb and VIc (Table 1) with 1,3-propanediol and 1,4-butanediol. Alcohol Va could also be

oxidized, albeit in poor yield, to its corresponding aldehyde.

TABLE 1.

PHYSICAL DATA OF ALCOHOLS V AND ACIDS VI

Product	Yield[a] (%)	Mp.[b] (dec.)	IR(KBr) (cm^{-1})	NMR,[c] δ	Anal., % Found (Calcd)
Va	97	210-212°	3450 1685	3.6-3.9(m,4H) 4.85(s,1H) 7.2-7.9(m,8H)	C,61.52(61.72) H,4.57(4.52) N,8.47(8.47) Cl, 10.56(10.74)
Vb	60	190-191°	3500 1690	1.6-2.0(m,2H) 3.4-4.0(m,4H) 4.75(s,1H) 7.2-7.8(m,8H)	C,62.72(62.69) H,4.97(4.96) N,7.98(8.12) Cl,10.03(10.29)
Vc	60	169-170°	3425 1690	1.4-1.8(m,4H) 3.2-3.9(m,4H) 4.77(s,1H) 7.2-7.8(m,8H) 10.8(br s,1H)	C,63.49(63.62) H,5.33(5.29) N,7.86(7.80) Cl, 9.89(9.89)
VIa	55	218-220°	3600-2500[d] 1730 1685	4.43(s,2H) 5.0(s,1H) 7.0-7.8(m,8H) 10.57(br s,1H)	C,59.08(59.21) H,3.90(3.77) N,8.23(8.12) Cl,10.41(10.30)
VIb	77	240-241°	3600-2500[d] 1720[e] 1690	3.7-4.2(m,4H) 4.80(s,1H) 7.2-7.8(m,8H) 10.55(br s,1H)	C,60.41(60.25) H,4.24(4.21) N,7.87(7.81) Cl,10.00(9.89)
VIc	70	226-227°	3600-2500[d] 1710[e] 1680	1.70-2.3(m,4H) 4.45(t,J=7Hz,2H) 4.72(s,1H) 7.2-8.2(m,8H)	C,60.88(61.23) H,4.62(4.56) N,7.61(7.51) Cl,9.55(9.52)

a) Isolated yields of pure material. b) Crystallized from acetonitrile. c) In DMSO-d_6 using TMS as an internal standard. d) Broad absorption band. e) Shoulder.

EXPERIMENTAL

Melting points were determined in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Solutions in organic solvents were dried over anhydrous magnesium sulfate. IR spectra were run on a Perkin-Elmer spectrophotometer. The NMR spectra were recorded on a Varian T-60 machine and the values are given in δ parts per million downfield from tetramethylsilane as an internal standard. A general method of preparation for benzodiazepine derivatives V and VI is given below.

3,7-Dichloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine (II). - To a stirred solution of freshly distilled thionyl chloride (1.6 g) and N,N-dimethylformamide (0.05 ml) at 0° was added in small portions oxazepam I (1.0 g) under nitrogen. A bright yellow solid precipitated. The reaction mixture was stirred for 1 hr. at 0°, then for 24 hr. at 4°. Excess thionyl chloride was removed under reduced pressure on a rotary evaporator. The last traces of thionyl chloride were removed by treating the yellow solid repeatedly with dry benzene and evaporating the solvent. The yellow solid was triturated with dry benzene and filtered with suction. The product was dried under vacuum to afford the chloro compound II (1.0 g, 95%) as a bright yellow solid, mp. 139-140° (dec.), lit.[2,3] mp. 120-121° (dec.) and 151-153° (dec.); NMR δ (DMSO-d_6) 6.1 (S, 1H), 7.2-7.9 (m, 8H), 9.7 (1H, concentration dependent) and 11.3 ppm.[4]

The yellow compound II reacted with water at room temperature to give oxazepam I as a colorless solid and with ethanol to give 7-chloro-2,3-dihydro-3-ethoxy-2-oxo-5-phenyl-1H-1,4-benzodiazepine (III), mp. 220°, lit.[2] mp. 225-227°.

Reaction of Chloro Compound II with Ethylene Glycol. Formation of 7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-

yloxy Ethanol (Va). - To vigorously stirred dry ethylene glycol (60 ml) under nitrogen was added in small portions the chloro compound II. After 4 hrs.,[5] the reaction mixture was diluted with excess water (200 ml) and extracted with chloroform. Evaporation of the dried organic extract afforded TLC pure hydroxy compound Va as a colorless solid (1.05 g, 97%) which when recrystallized from acetone melted at 216-217°. IR (KBr) 3450 (OH), 3100 (NH), 1685 (C=O) cm^{-1}, NMR (DMSO-d_6) δ 3.6-3.9 (m, 4H, $-OCH_2-CH_2-$), 4.85 (s, 1H, C-3 methine), 7.2-7.9 (m, 8H, aromatic protons).

Anal. Calcd for $C_{17}H_{15}ClN_2O_3$: C, 61.72; H, 4.54; N, 8.47; Cl, 10.74. Found: C, 61.52; H, 4.57; N, 8.47; Cl, 10.56.

The alcohols Vb and Vc were obtained by the above method using a slightly modified work up procedure. Thus, after the chloro compound II had reacted with 1,3 propanediol or 1,4-butanediol the product was isolated with chloroform. The solvent was removed and the residue triturated with a small amount of ether. The solid was recrystallized from acetonitrile to afford the pure products Vb and Vc.

Oxidation of Alcohol Va with Jones Reagent. Preparation of 7-Chloro-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-yloxy Acetic Acid (VIa). - To an ice-cold solution of alcohol Va (0.5 g) in acetone (125 ml, distilled over $KMnO_4$) was added excess Jones reagent.[6] The reaction mixture was stirred at 0° for 1 hr. After an additional stirring for 60 min. at room temperature the reaction mixture was poured into 500 ml of ice-cold water and the product was extracted with ethyl acetate. The organic layer was extracted with 5% aqueous

sodium bicarbonate solution. The bicarbonate solution was cooled to 0°, acidified to pH 3 with dil. hydrochloric acid and was thoroughly extracted with ethyl acetate. Removal of the organic solvent from the dried extract gave the acid VIa (330 mg, 65%, mp. 205-207°). Recrystallization from acetonitrile afforded analytically pure VIa, mg. 218-220° (dec.) lit.[1c] mp. 205-207°. IR (KBr) : 2500-3650 (OH and NH), 1730 (-C-OH), 1685 (-C-NH); NMR (DMSO-d_5) δ 4.43 (s, 2H, $-OCH_2-$), 5.0 (s, 1H, C-3 methine), 7.2-7.9 (m, 8H, aromatic protons), 10.6 (br. s, 1H, COOH).

Anal. Calcd. for $C_{17}H_{13}ClN_2O_4$: C, 59.21; H, 3.77; N, 8.12; Cl, 10.30. Found: C, 59.08; H, 3.90; N, 8.23; Cl, 10.41.

The acid VIa was further characterized as its benzamide derivative, mp. 187-188°; NMR ($CDCl_3$) δ 4.5 (s, OCH_2), 4.6 (d, J = 5 Hz, $-NHCH_2$) [total 4H], 4.88 (s, 1H, C-3 methine), 7.2-7.8 (m, 8H aromatic protons), 10.0 (br s, NH).

Anal. Calcd. for $C_{24}H_{20}ClN_3O_3$: C, 66.43; H, 4.61; N, 9.68; Cl, 8.19. Found: C, 66.01; H, 4.75; N, 9.63; Cl, 8.23.

Acknowledgements. Helpful discussions with Dr. Edwin F. Ullman are gratefully acknowledged.

REFERENCES

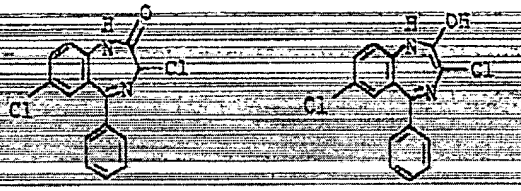
† Syva Contribution #70.

1. a) G. A. Archer and L. H. Sternbach, Chem. Rev., 68, 747 (1968); b) L. H. Sternbach, Angew. Chem. Internat. Edit., 10, 34 (1971); c) S. C. Bell, R. J. McCaully, C. Gochman, S. J. Childress and M. I. Gluckman, J. Med Chem., 11, 457 (1968).
2. S. C. Bell and S. J. Childress, J. Org. Chem., 27, 1961

(1962).

3. T. Kovac, P. Kajfez, V. Sunjic and M. Oklobdzija, J. Med. Chem., 17, 766 (1974).

4. A low field signal at δ 11.3 ppm in NMR spectrum of II and its yellow color strongly indicates its existence in equilibrium with enol IIa.



II IIa

5. The reaction was found, by silica tlc, to be essentially complete within few minutes.

6. L. F. Fieser and M. Fieser "Reagents for Organic Synthesis", Vol. 1, John Wiley, New York, N.Y., 1967, p. 142.

7. Prepared by treating the acid with isobutyl chloroformate in the presence of triethylamine followed by treatment of the mixed anhydride with benzylamine.

(Received November 14, 1977; in revised form February 21, 1978)